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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/037,791	01/03/2002	Stanley M. Crain	96700/727	7711

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EXAMINER	
JONES, DWAYNE C	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 02/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/037,791	CRAIN ET AL.	
	Examiner	Art Unit	
	Dwayne C Jones	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-99* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-99* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 30-99 are pending.

2. Claims 30-99 are rejected.

Response to Arguments

3. Applicants' arguments filed August 18, 2003 have been fully considered but they are not persuasive. Applicants present the following arguments. First, applicants argue that Levine et al. do not teach of the administration of an excitatory opioid receptor antagonist in an amount effective to enhance the analgesic potency of an opioid agonist. Second, applicants argue that pentazocine is known to be a mixed agonist/antagonist activity. Third, applicants purport that Lewenstein et al. do no disclose or suggest the administration of an antagonist in an amount effective to enhance the analgesic potency of an agonist. Fourth, applicants allege that Patcher et al. of U.S. Patent No. 3,879,555 as well as Patcher et al. of U.S. Patent No. 3,773,955 do not teach of the administration of an antagonist in an amount effective to enhance the analgesic potency of an antagonist, but rather teach that the antagonist blocks the analgesia of an agonist. Fifth, applicant argues that the phrase, "similarly acting" is defined.

4. First, applicants argue that Levine et al. do not teach of the administration of an excitatory opioid receptor antagonist in an amount effective to enhance the analgesic potency of an opioid agonist. Levine et al. specifically teach of the administration of

pentazocine with the low dose administration of naloxone in order to treat pain as well as produce significantly greater analgesia than with either low-dose naloxone or pentazocine.

5. Second, applicants argue that pentazocine is known to be a mixed agonist/antagonist activity. The instant invention is claiming the administration of two components (1) an opioid agonist and (2) an opioid receptor antagonist. The instant application recites inter alia that pentazocine is an example of an opioid agonist, and that naloxone is an example of an opioid receptor antagonist. The prior art reference of Levine et al. also teaches of the administration of pentazocine accompanied with the low dose administration of naloxone, (see page 1575). In addition, Levine et al. also teach of the combined administration of morphine with low dose naloxone. Accordingly, the attenuation of tolerance associated with pentazocine or even morphine for that matter, must be an inherent property or benefit of the methods taught by the prior art, namely Levine et al.

6. Third, applicants purport that Lewenstein et al. do no disclose or suggest the administration of an antagonist in an amount effective to enhance the analgesic potency of an agonist. Lewenstein et al. specifically teach of the administration of a composition that is comprised of morphine and naloxone in dosages that are approximately between 300 to 10 fold less of the naloxone when compared to morphine. In fact, Lewenstein et al. teach that this composition provides strong analgesic effects without the occurrence of undesired or dangerous side effects. Lewenstein et al. also teach of various modes and methods of administration of these compositions to treat pain.

7. Fourth, applicants allege that Patcher et al. of U.S. Patent No. 3,879,555 as well as Patcher et al. of U.S. Patent No. 3,773,955 do not teach of the administration of an antagonist in an amount effective to enhance the analgesic potency of an antagonist, but rather teach that the antagonist blocks the analgesia of an agonist. This allegation is unfounded. Patcher et al. specifically teach, that "[a] preferred embodiment of the present invention is an orally effective, analgetic composition which, upon parenteral administration, does not produce analgesia, euphoria or physical dependence", (see column 5, lines 38-41 of U.S. Patent No. 3,879,555; and Patcher et al. of U.S. Patent No. 3,773,955 in column 6, lines 53-60). In addition, Patcher et al. specifically recite using the opioid agonists inter alia, methadone, codeine, fentanyl, pentazocine, and morphine, (see from column 5, line 66 to column 6, line 25 of U.S. Patent No. 3,879,555; and Patcher et al. of U.S. Patent No. 3,773,955 from column 3, line 55 to column 4, line 12). Furthermore, it is noted that Patcher et al. define the term of "strong analgetic" as any analgetic agent whose analgetic, euphoric or dependence producing actions are negated by the parenteral administration of compound I, which is naltrexone. Patcher et al. also define "strong analgetics" as to the often referred "narcotic-like analgetics" that are also defined herein as including those chemical agents which upon parenteral administration are capable of maintaining or partially maintaining a known addict to heroin or the like without substantial withdrawal symptoms, (see column 3, lines 45-56 of Patcher et al. of U.S. Patent No. 3,879,55; and Patcher et al. of U.S. Patent No. 3,773,955 in column 3, lines 9-33).

8. Fifth, applicant argues that the phrase, "similarly acting" is defined. It is still unclear in this particular patent application what the phrase, "similarly acting" is referring to, namely opioid alkaloids and opioid peptides or to the activities of these agonists.

Information Disclosure Statement

9. The information disclosure statement filed on December 6, 2002 has been reviewed and considered, see enclosed copies of PTO FORMs 1449.

10.

Claim Rejections - 35 USC § 112

11. The rejection of claims 32 and 42 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained for both the above-stated and reasons of record.

Claim Rejections - 35 USC § 102

12. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

13. The rejection of claims 30-33, 36, 40-44, 46, 52, 68, 70, 71, 78, 79, 95, 97, and 98 under 35 U.S.C. 102(b) as being anticipated by Levine et al. is maintained for both the reasons of record and those cited above in this Office action.

14. The rejection of claims 30-32, 36, 52, and 71 under 35 U.S.C. 102(b) as being anticipated by Lewenstein et al. of U.S. Patent No. 3,493,657 is sustained for both the reasons of record and those cited above in this Office action.

15. The rejection of claims 30-40, 53, 66, and 70 under 35 U.S.C. 102(b) as being anticipated by Pachter et al. of U.S. Patent No. 3,879,555 is maintained for both the reasons of record and those cited above in this Office action.

16. The rejection of claims 30-33, 36, 38-40, 52, 68, and 70 under 35 U.S.C. 102(b) as being anticipated by Pachter et al. of U.S. Patent No. 3,879,955 is maintained for both the reasons of record and those cited above in this Office action.

Claim Rejections - 35 USC § 103

17. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

18. The rejection of claims 30-33, 36, 40-44, 46, 52, 68, 70, 71, 78, 79, 95, 97, and 98 under 35 U.S.C. 103(a) as being unpatentable over Lewenstein of U.S. Patent No. 3,493,657 is maintained for both the above-stated and reasons of record.

19. The rejection of claims 41-48, 76, 77, 79, 80, 93, 97, and 98 under 35 U.S.C. 103(a) as being unpatentable over Pachter et al. of U.S. Patent No. 3,879,555 is maintained for both the above-stated and reasons of record.

20. The rejection of claims 30-33, 36, 38-44, 46, 52, 68, 70, 76-80, 95, and 97 under 35 U.S.C. 103(a) as being unpatentable over Pachter et al. of U.S. Patent No. 3,879,955 is maintained for both the above-stated and reasons of record.

21. Claims rejected 30-33, 36, 40-44, 46, 49-52, 54, 56, 58, 64, 68, 70, 71, 73-75, 78, 79, 81, 83, 85, 91, 95, 97, and 98 under 35 U.S.C. 103(a) as being unpatentable over Lewenstein of U.S. Patent No. 3,493,657 in view of Goodman & Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 9th Edition. Lewenstein teaches of the modes of administration, iv, im, sc, for the compositions of naloxone and strong analgesic, (see column 2, lines 70-73; column 3, line 9). It would have been obvious to one of ordinary skill in the art to utilize the composition as taught by Lewenstein to administer via well known established method to treat patients suffering pain since the references exemplify such parenteral routes to administer analgesic compositions, wherein the analgesics were well known to treat pain with a reasonable expectation of relieving pain with morphine compositions, without the unwanted side effects of morphine as taught by the reference. The use of the composition in the method taught by the reference wherein the ratio of morphine to naloxone is at least 100:1 would have been obvious since the reference teaches an overlapping useful range of 10 to 300 fold less of the naloxone as being effective, in the absence of evidence of criticality or unexpected results. In Goodman & Gilman's teaches that morphine has activities on both mu and kappa receptor sites; methadone and fentanyl have affinity for the mu receptor site; Met-enkephalin and Leu-enkephalin have affinities for both the mu and delta sites; dynorphin B has affinity for mu, delta and kappa receptor sites; and the beta-

endorphin has activity at the mu and delta receptor sites, (see pages 523-526). Accordingly, the treatment of pain would obviously embrace chronic pain to one having ordinary skill in the art. In addition, the naming of a receptor site, namely mu, delta and kappa, that has affinity with a particular opioid receptor agonist or opioid receptor antagonist is well established in the pharmaceutical art, (see Goodman & Gilman's). Clearly, it would have been obvious to the skilled artisan to specify the well-known receptor sites of well-established opioid agonists and opioid antagonists.

22. Claims 30-51, 53, 55, 57, 59, 62, 65, 71, 73-77, 79, 80, 82, 84, 86, 89, 93, 97, and 98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Patcher et al. of U.S. Patent No. 3,879,555 in view of Goodman & Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 9th Edition. Pachter et al. teach of methods of treating drug addictions with orally effective analgesic compositions comprising opioid agonists in combination with opioid antagonist, (see column 4, lines 11-55, column 6, lines 34, 39-44, and column 11, example 7). Pachter et al. do not particularly exemplify a method for treating pain, however, Pachter et al. do teach of a method for producing analgesia and disclose that the utility of the analgesics in the treatment of various conditions, (see column 2, lines 13-34 and column 7, lines 58-67). It would have been obvious to one skilled in the art to apply the method of Pachter et al. to treat pain since it is well recognized in the art to relieve pain with opioid analgesics. Since the reference teaches that the methods of using the analgesics in combination with antagonist naltrexone prevent the well-known adverse side effects, one skilled in the art would have been motivated to apply Pachter et al. method in treating pain, with a reasonable

expectation of obtaining pain relief without the addiction potential. In Goodman & Gilman's teaches that morphine has activities on both mu and kappa receptor sites; methadone and fentanyl have affinity for the mu receptor site; Met-enkephalin and Leu-enkephalin have affinities for both the mu and delta sites; dynorphin B has affinity for mu, delta and kappa receptor sites; and the beta-endorphin has activity at the mu and delta receptor sites, (see pages 523-526). Accordingly, the treatment of pain would obviously embrace chronic pain to one having ordinary skill in the art. In addition, the naming of a receptor site, namely mu, delta and kappa, that has affinity with a particular opioid receptor agonist or opioid receptor antagonist is well established in the pharmaceutical art, (see Goodman & Gilman's). Clearly, it would have been obvious to the skilled artisan to specify the well-known receptor sites of well-established opioid agonists and opioid antagonists.

23. Claims 30-33, 36, 38-44, 46, 49-54, 56, 58, 64, 68, 70, 71, 73-81, 83, 85, 91, 95, 97, and 98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Patcher et al. of U.S. Patent No. 3,773,955 in view of Goodman & Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 9th Edition. Pachter et al. disclose of a method of treating drug addicts with a composition comprising opioid agonists in combination with naloxone as a potent, orally effective, but parenterally inactive analgesic medicine useful for treatment of various conditions without addiction and to reduce drug abuse potential. The reference teaches that the strong analgesic opioid agonists are known to provide relief of severe pain but usually produce euphoric effect on parenteral administration and lead to addiction and abuse. Pachter et al. invented a

composition that contains a parenterally effective but orally ineffective dose of opioid antagonist such as naloxone and an orally analgesic dose of an orally effective strong analgesic such that the composition can be administered orally and not interfere with the analgesic effect of the opioid agonist. These compositions may be administered parenterally without causing euphoria. The effective dosage ratios taught by Pachter et al. must inherently produce the claimed benefits sought by the instant application since the two methods are the same. In addition, Pachter et al. further disclose that the strong analgesics have been employed in the relief of more severe pain but that they usually produce a euphoric effect on parenteral administration. It would be obvious to one skilled in the art to use the composition, as taught by Pachter et al., in order to relieve pain since the composition does not produce the adverse euphoric side effects. Furthermore, the use of the analgesic composition of greater than 100 fold more than antagonist in such a method would have been obvious in view of the Pachter et al. for about 80 parts pentazocine and up to 150 codeine with one part naloxone, in the absence of criticality to the claimed ranges. In Goodman & Gilman's teaches that morphine has activities on both mu and kappa receptor sites; methadone and fentanyl have affinity for the mu receptor site; Met-enkephalin and Leu-enkephalin have affinities for both the mu and delta sites; dynorphin B has affinity for mu, delta and kappa receptor sites; and the beta-endorphin has activity at the mu and delta receptor sites, (see pages 523-526). Accordingly, the treatment of pain would obviously embrace chronic pain to one having ordinary skill in the art. In addition, the naming of a receptor site, namely mu, delta and kappa, that has affinity with a particular opioid receptor

agonist or opioid receptor antagonist is well established in the pharmaceutical art, (see Goodman & Gilman's). Clearly, it would have been obvious to the skilled artisan to specify the well-known receptor sites of well-established opioid agonists and opioid antagonists.

Obviousness-type Double Patenting

24. The rejections of claims 30-99 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-32 of U.S. Patent No. Re 36,547; claims 1-31 of U.S. Patent No. 6,362,194; claims 1-18 of U.S. Patent No. 5,767,125; and claims 1-10 of U.S. Patent No. 5,472,943 are withdrawn in response to the filing of the Terminal Disclaimers (TD), respectively. Note that applicant correctly filed a TD for U.S. Patent No. 5,767,125 instead of the typographic mistake of U.S. Patent No. 5,762,125, as incorrectly listed in the Office action of February 19, 2003.

25. However, the rejection of claims 30-99 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 6,096,756 in view of Goodman & Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 9th Edition, is maintained because both the instant invention and the U.S. Patent No. 6,096,756 are directed to the treatment of pain with the coadministration of an opioid antagonist and an opioid agonist. In Goodman & Gilman's teaches that morphine has activities on both mu and kappa receptor sites; methadone and fentanyl have affinity for the mu receptor site; Met-enkephalin and Leu-

enkephalin have affinities for both the mu and delta sites; dynorphin B has affinity for mu, delta and kappa receptor sites; and the beta-endorphin has activity at the mu and delta receptor sites, (see pages 523-526). Accordingly, the treatment of pain would obviously embrace chronic pain to one having ordinary skill in the art. In addition, the naming of a receptor site, namely mu, delta and kappa, that has affinity with a particular opioid receptor agonist or opioid receptor antagonist is well established in the pharmaceutical art, (see Goodman & Gilman's). Clearly, it would have been obvious to the skilled artisan to specify the well-known receptor sites of well-established opioid agonists and opioid antagonists.

Conclusion

26. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. C. Jones whose telephone number is (571) 272-0578. The examiner can normally be reached on Mondays, Tuesdays, Thursday, and Fridays from 8:30 am to 6:00 pm. The official fax No. for correspondence is (703) 872-9306.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel, may be reached at (571) 272-0584.

DWAYNE JONES
PRIMARY EXAMINER

Tech. Ctr. 1614
February 23, 2004